

Rapid Tranquilization of Severely Agitated Patients With Schizophrenia Spectrum Disorders

A Naturalistic, Rater-Blinded, Randomized, Controlled Study With Oral Haloperidol, Risperidone, and Olanzapine

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Introduction: Agitation is a major problem in acute schizophrenia. Only a few studies have tested antipsychotic agents in severely agitated patients, mainly because of legal issues. Furthermore, most studies were limited to the first 24 hours. We aimed to investigate the efficacy of oral haloperidol, risperidone, and olanzapine in reducing psychotic agitation in severely agitated patients with schizophrenia or schizophreniform or schizoaffective disorder over 96 hours using a prospective, randomized, rater-blinded, controlled design within a naturalistic treatment regimen. **Methods:** In total, 43 severely agitated patients at acute care psychiatric units were enrolled. Participants were randomly assigned to receive either daily haloperidol 15 mg, olanzapine 20 mg, or risperidone 2 to 6 mg over 5 days. Positive and Negative Syndrome Scale psychotic agitation subscale score was the primary outcome variable. A mixed-model analysis was applied.

Results: All drugs were effective for rapid tranquilization within 2 hours. Over 5 days, the course differed between agents ($P < 0.001$), but none was superior. Dropouts occurred only in the risperidone and olanzapine groups. Men responded better to treatment than did women during the initial 2 hours ($P = 0.046$) as well as over the 5-day course ($P < 0.001$). No difference between drug groups was observed regarding diazepam or biperiden use.

Conclusions: Oral haloperidol, risperidone, and olanzapine seem to be suitable for treating acute severe psychotic agitation in schizophrenia spectrum disorders. Response to oral antipsychotics demonstrated a gender effect with poorer outcome in women throughout the study.

Key Words: aggressive behavior, agitation, schizophrenia, rapid tranquilization, haloperidol, risperidone, olanzapine

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Aggression and agitation are frequent problems during acute schizophrenia episodes.^{1,2} Aggressive behavior in inpatient settings is associated with involuntary admission and schizophrenia diagnosis.^{3–5} Interestingly, some studies reported women

to exert more aggressive behavior during the acute inpatient treatment than men.^{5,6}

Both agitation and aggressive behavior represent psychiatric emergencies requiring rapid intervention to prevent harm to the patient, staff, or other subjects. A number of nonpharmacological interventions have been suggested, such as talking down or clearing the room of other patients.⁷ Pharmacological treatment of agitation and aggression in schizophrenia should aim at calming the patient while treating the underlying psychosis.^{1,2} Therefore, clinical guidelines recommend parenteral administration of typical antipsychotics in combination with benzodiazepines as the first line for rapid tranquilization.^{8,9} In addition to parenteral antipsychotics, oral administration of second-generation antipsychotics has proven efficacious in reducing acute agitation, as has been reported for risperidone, olanzapine, aripiprazole, and quetiapine.^{10–15} Most previous studies on acute agitation in mixed patient populations report outcomes only in the first 24 to 72 hours after admission,^{12,13,15–17} and only a few studies extend over 5 days.^{11,14} However, efficacy of antipsychotic agents may vary widely over an observation period, with some exhibiting superior performance only during the initial hours.^{11,13} Despite this, we are unaware of any trials comparing oral formulations of first- and second-generation antipsychotics beyond the first day in acutely agitated schizophrenia patients. Furthermore, interventional trials must obtain prior informed consent from study participants, precluding prospective studies in severely agitated or aggressive patients. Thus, most studies on pharmacotherapy of acute schizophrenia episodes have been conducted in patients with low agitation scores.

In the current study, we try to overcome these 2 problems by investigating the effects of 3 oral antipsychotics (haloperidol, olanzapine, and risperidone) on psychotic agitation in severely agitated patients with schizophrenia spectrum disorders during the first 5 days after admission and obtaining informed consent for inclusion in the study after remission of the psychotic episode. The study was a prospective, randomized, rater-blinded trial in a naturalistic treatment setting and regimen. Based on independently reported results in the literature, we hypothesized superior performance of olanzapine and haloperidol during the initial 2 hours, as well as a reduced need for additional benzodiazepines with olanzapine administration. In addition, because of reported diminished effect of antipsychotics in women, we examined gender effects on treatment response.

PATIENTS AND METHODS

Participants

From February 2004 until September 2005, all patients admitted to the acute care inpatient units of the University Hospital of Psychiatry Bern, Switzerland, were screened for schizophrenia, schizoaffective, or schizophreniform disorder according to the

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Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria. Diagnoses were made based on psychiatric examination and review of all case files. Only subjects aged between 18 and 55 years were further evaluated. Subjects with relevant medical or neurological disorders, who were pregnant, or who had ongoing intake of illicit drugs and alcohol were excluded.

Assessments

Symptom severity was assessed using the Positive and Negative Syndrome Scale (PANSS).¹⁸ We used the PANSS psychotic agitation subscale (PANSS-PAS) including PANSS items *hallucinatory behavior* (P3), *excitement* (P4), *hostility* (P7), *uncooperativeness* (G8), and *poor impulse control* (G14) to select subjects who were highly agitated. The PANSS-PAS was used in previous studies¹⁰ and is similar to the PANSS excitement subscale used in comparable studies on agitation,^{19,20} with a range of 5 to 35 points. Further assessments included the Abnormal Involuntary Movement Scale (AIMS),²¹ the Simpson Angus Scale for Parkinsonism (SAS),²² and the Barnes Akathisia Rating Scale (BARS).²³

Procedures

Subjects scoring 20 (eg, moderate symptom severity in each of the 5 items) or higher on the PANSS-PAS were randomly assigned to 1 of the 3 treatment regimens. As it was not possible to obtain informed consent at the time of study inclusion due to severe agitation, an independent psychiatric consultant had to clinically confirm whether the study criteria were met. Randomized treatment allocation was permitted since the protocol strictly followed the Swiss registration guidelines for antipsychotics, and none of the 3 oral substances has proven superiority in treating agitation. After remission of the acute symptoms and regaining the capacity to understand the study procedures, subjects were asked for written consent to participate in the study. Only data from participants who provided post hoc consent were included in study analyses (see Figure S1, Supplemental Digital Content 1, <http://links.lww.com/JCP/A218>). This approach is in line with the World Medical Association Declaration of Helsinki. The local ethics committee approved the study protocol.

In total, 6 study visits were conducted over a total of 5 days. On day 1, 2 visits occurred: at baseline (T0) and 2 hours later (T1). Additional visits randomly took place within 24 hours (T2), 48 hours (T3), 72 hours (T4), and 96 hours (T5) after baseline. The PANSS-PAS was assessed at each visit, and the complete PANSS was evaluated at T0 and T5. The AIMS, BARS, and SAS were rated at T5. All ratings were performed by 1 of 2 raters who were blind to treatment allocation, had received PANSS training, and had no access to the randomization protocol. Randomization was performed by creating 3 sets of random numbers between 1 and 60 using a computer-based research randomizer (www.randomizer.org). The order of inclusion determined allocation to treatment group. The randomization list was locked in the office of the principal investigator (T.J.M.), who was engaged neither in treatment nor in study assessments.

Swiss registration guidelines on antipsychotic administration were strictly adhered to as follows: on the first day, 10 mg haloperidol, 2 mg risperidone, or 15 mg olanzapine were administered as regular tablets. The additional use of up to 30 mg diazepam was permitted. From days 2 through 5, fixed doses of haloperidol (7.5 mg twice daily [BID]) and olanzapine (20 mg) were given, whereas risperidone doses were 2 mg BID on day 2 and 3 mg BID on day 3. Subsequently, risperidone doses could be increased by 1 mg/d at the discretion of the independent psychiatric consultant. The additional use of up to 60 mg diazepam

was permitted from days 2 through 5. In case the additional medication was not sufficient to control agitation, subjects received higher doses of parenteral typical antipsychotics and diazepam and were considered dropped from the study because of lack of efficacy.

Statistical Analyses

Analyses were based on the intent-to-treat model. χ^2 Tests for categorical data and analysis of variance for continuous data were computed to compare baseline characteristics between the 3 medication groups. Courses of tranquilization from T0 to T5 were analyzed by a mixed model of repeated measures with PANSS-PAS as the primary outcome, time as the random factor, and type of medication as the fixed factor. Total dose of diazepam and total dose of biperiden prescribed during the observation period (T0–T5) were included as covariates to statistically control their effect on psychotic agitation. Main (time and medication) and interaction (time \times medication, time \times diazepam, and time \times biperiden) effects were tested. Rapid tranquilization within 2 hours was analyzed by an analysis of covariance (ANCOVA) with the same variables as used in the mixed model but only for the 2 assessments within the first day. Again, main and interaction effects were tested. Finally, the same analyses for rapid and course of tranquilization were performed, with gender as the fixed factor. Other outcome variables were compared using analyses of variance or χ^2 tests. For these other outcome variables, the last observation carried forward method was applied to data of patients who were prematurely dropped from the study. All analyses were computed with the Statistical Package for the Social Sciences (SPSS 19; SPSS Inc, Chicago, IL).

RESULTS

In total, 52 subjects were eligible for inclusion. Post hoc consent was provided by 43 subjects (83%), whose data were included in the analyses. The final analyses included 14 subjects on haloperidol, 15 on olanzapine, and 14 on risperidone. The groups did not differ in clinical or demographic variables. Patients were predominantly male (72%). Eleven had immigrant status. Diagnoses included paranoid ($n = 18$), disorganized ($n = 5$), catatonic ($n = 1$), and residual ($n = 3$) schizophrenia, as well as schizophreniform ($n = 10$) and schizoaffective ($n = 6$) disorder. Mean age was 34.4 (SD, 10.1) years, duration of illness was 6.9 (SD, 6.6) years, and duration of education was 11.6 (SD, 2.5) years. Before admission, 4 participants had consumed alcohol, and 5 have used cannabis. The average PANSS scores were as follows: positive, 36.1 (SD, 5.2); negative, 25.5 (SD, 8.4); PAS, 26.4 (SD, 3.4); EC, 28.0 (SD, 4.1); and total score, 126.7 (SD, 16.9).

Of the 43 subjects, 36 (83.7%) were free of antipsychotics or mood stabilizers at the time of study inclusion with no differences between the 3 treatment groups. Whereas the olanzapine and haloperidol groups received a fixed dose, the risperidone group received varying antipsychotic dosage after the first day. Mean daily risperidone doses were the following: day 2: 3.7 (SD, 1.1) mg; day 3: 5.5 (SD, 1.7) mg; day 4: 5.5 (SD, 1.7) mg; day 5: 5.5 (SD, 1.7) mg. Six subjects (13.9%) were dropped from the study because of lack of efficacy. Of those who were dropped, 4 subjects were on risperidone (2 on day 1, 1 on day 3, 1 on day 5), and 2 were on olanzapine (1 on day 1 and 1 on day 5).

PANSS-PAS Scores

Rapid tranquilization effects were analyzed for the first 2 hours (see Table S1, Supplemental Digital Content 2, <http://links.lww.com/JCP/A219>). The PANSS-PAS scores improved with any medication, as we noted an effect of time ($P < 0.001$), but neither effect of medication nor a time \times medication interaction. Furthermore, the administration of diazepam

or biperiden did not affect the effects of antipsychotic medication on PANSS-PAS. Moreover, we noted a gender effect ($P = 0.046$) indicating that men responded better to treatment than did women in the first 2 hours.

Regarding the PANSS-PAS score over the 5-day course of the study, we observed a significant effect of time ($P < 0.001$) as well as a significant medication \times time interaction ($P < 0.001$; Fig. 1). Post hoc ANCOVAs with gender and diazepam and biperiden cumulative doses as covariates indicated significant differences between antipsychotics at T3 ($P = 0.009$) and T4 ($P = 0.031$), as well as trends for T1 ($P = 0.053$), T2 ($P = 0.092$), and T5 ($P = 0.074$), without significant differences in the single substance contrasts at any time point. Furthermore, in the mixed model, PANSS-PAS scores were affected by the interaction of gender \times time ($P < 0.001$), demonstrating that women never improved as much as men (see Figure S2, Supplemental Digital Content 3, <http://links.lww.com/JCP/A220>). No other effect was significant, including factors such as antipsychotic drug, diazepam, biperiden, and their interaction terms with time. Post hoc ANCOVAs with antipsychotic drug, diazepam, and biperiden cumulative doses as covariates indicated significantly less PANSS-PAS reduction in women at T1 ($P = 0.046$), T3 ($P = 0.004$), and T4 ($P = 0.020$), as well as a trend at T2 ($P = 0.056$). Adding the duration of illness as a covariate did not change the results of these primary analyses (data not shown).

Additional Outcome Measures

Possible motor adverse effects did not differ between groups at T5 in scores of BARS, SAS, and AIMS. Furthermore, the use of additional medication was not different between groups (see Table S2, Supplemental Digital Content 4, <http://links.lww.com/JCP/A221>). Comparing the PANSS-EC at T0 and T5, we found a significant effect of time ($P < 0.001$), but no effect of antipsychotic agent and no interaction effect. Results did not change after controlling for diazepam administration.

Diazepam was administered to 37 subjects (86%) within the first 24 hours. The mean cumulative dose for the first 24 hours was 25.6 (SD, 17.0) mg, with no difference between groups. During the study period, severe agitation led to use of seclusion in 2 subjects (1 on haloperidol and 1 on olanzapine) and to the

use of physical restraints in 9 subjects (2 on haloperidol, 4 on risperidone, and 3 on olanzapine).

DISCUSSION

In the present study, oral administration of haloperidol, olanzapine, or risperidone was highly effective in reducing psychotic agitation in schizophrenia within 2 hours. The course over 5 days differed between antipsychotic substances used, but post hoc analyses favored none of the agents. Interestingly, men responded better to treatment than did women throughout the course of the study.

Our findings regarding the rapid tranquilization in severely agitated schizophrenia are in line with previously published work.^{10–13} Most studies have reported no differences between substances in the first 2 hours after administration.^{11–13} Recently, Hsu et al¹³ noted a superior performance of olanzapine over haloperidol during the first 90 minutes; however, they found no differences in the efficacy of haloperidol intramuscularly (IM), olanzapine IM, olanzapine oral disintegrating tablets, and risperidone oral solution after 24 hours. The slight difference to the study of Hsu et al,¹³ which found superior effects for olanzapine only in the first 90 minutes, may stem from the participant selection. Even though the PANSS-EC scores indicate comparable symptom severity, the trial of Hsu et al¹³ included patients with bipolar I disorder (43%). Taken together, rapid tranquilization in acutely agitated schizophrenia patients may be achieved by any of the tested antipsychotics even when administered orally. However, it remains unclear whether PANSS-PAS reduction within the first 2 hours is achieved by specific antipsychotic action or by sedative properties of antipsychotic substances. Use of additional diazepam was frequent and not different between groups.

Even though all 3 agents effectively reduced agitation over 5 days, the course differed between groups, particularly at days 3 and 4. However, the post hoc tests did not reveal a significant difference between the agents at any time point. Two controlled trials over 5 days also reported no difference between oral aripiprazole and oral olanzapine¹⁴ and between oral risperidone and intramuscular haloperidol.¹¹ Likewise, an observational, nonrandomized study in a mixed psychiatric emergency population failed to find differences between olanzapine, risperidone, and haloperidol over 5 days.²⁴ In contrast, longer trials seem to favor olanzapine. A 3-year observational study documented lesser violence in patients on olanzapine maintenance than in risperidone-treated patients.²⁵ Likewise, post hoc analyses from larger 6-week trials indicated superior improvement of psychotic agitation with oral olanzapine compared with oral haloperidol.²⁶ We noted differences between substances over a 5-day course of treatment, but the variance is not systematically related to a single antipsychotic agent.

With both second-generation antipsychotics, subjects were dropped from the study because of lack of efficacy. Four dropouts were in the risperidone group and 2 in the olanzapine group. One explanation could be that the dose regimen of risperidone included rather low doses on the first and second days. Although the present study followed the Swiss registration guidelines, it is conceivable that the outcome was dependent on the dosages used. The haloperidol doses used in other trials were lower for oral formulations (range, 10–15 mg/d)¹⁵ and in the same range for IM formulations (range, 5–20 mg/d).^{10–13} The olanzapine dosage used was comparable to that used in other trials (range, 10–20 mg/d),^{13–15,27} whereas the risperidone dosage in the first 2 days was lower than the dose in other trials (range, 2–6 mg).^{11–13} Thus, the dose regimen applied in this study may have contributed to better performance of haloperidol in

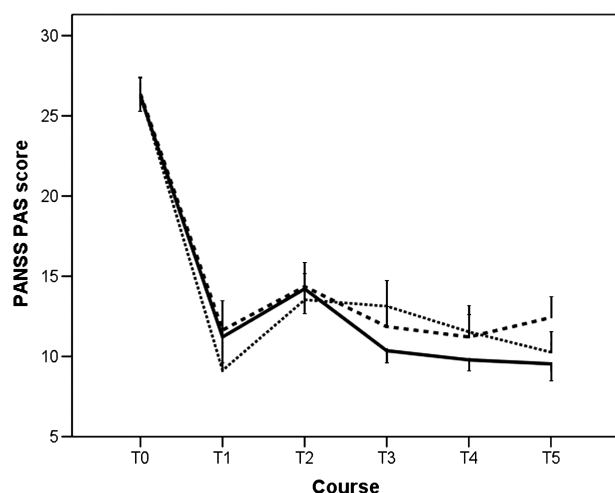


FIGURE 1. Agitation scores. Mean and SEM of PANSS-PAS scores are depicted. Solid line: haloperidol, dashed line: risperidone, dotted line: olanzapine.

terms of the number of subjects dropped from the study. The frequency of seclusion or physical restraints, however, did not differ between the groups.

In the present study, we observed a gender effect indicating that women did not respond to antipsychotic treatment as well as men did. Differences between genders were noted consistently from the first rating after baseline (2 hours) until T4 (3 days). Thus, throughout the initial 72 hours, men showed more favorable outcomes. The gender difference in aggressive behavior is increasingly acknowledged. Women displayed proportionally more aggressive behavior than did men in the initial 4 weeks of inpatient treatment,^{5,6,28} whereas during longer hospitalization this difference disappears.^{4,6} This gender effect of the early inpatient period could contribute to the poor treatment response in women observed in our study. Furthermore, men might be more compliant in these emergencies. When given the choice of oral versus IM medication, men chose oral medication during severe agitation more frequently than did women.¹⁰ To the contrary, a study reported pronounced reductions of assaults with treatment in women compared with men,⁶ linking positive symptom severity and aggression, particularly in women. However, this study compared treatment efficacy between groups after 4 weeks.

This study design limited the selection bias due to a refusal to participate in the acute psychotic state. Nonetheless, 17% of the patients initially randomized declined post hoc consent for study inclusion. We have, however, included a representative portion of the highly agitated psychotic patients admitted to our department. This is a clear strength of the study. The severity of agitation as measured with the PANSS-EC is in the same range as reported in 1 controlled trial and 3 observational studies^{10,13,24,27} but clearly higher than in most controlled trials.^{11,12,14} We have used higher PANSS cutoff scores for inclusion than the cutoff used in most other studies.^{11–13,20} Furthermore, we restricted our sample to schizophrenia spectrum disorders, excluding patients with bipolar disorder who represent a considerable proportion in some trials.^{12,13,27}

The main limitation of this study is the limited number of participants, which is not sufficient to support noninferiority conclusions of 1 of the antipsychotic agents used. Furthermore, the acute and agitated presentation at baseline prevented us from conducting comprehensive assessments of psychosocial function or pretreatment motor disorders. Therefore, we cannot comment on treatment-emergent motor adverse effects. Furthermore, there is a potential risk of diagnostic bias as the diagnoses were not established in structured interviews, mainly because of time limitations at inclusion. As discussed above, a change in dose regimen may have resulted in slightly different effects, as the initial risperidone dose is lower than that used in other trials.^{11–13}

Oral administration of haloperidol 10 mg, olanzapine 15 mg, or risperidone 2 mg was highly effective in reducing psychotic agitation in patients with schizophrenia spectrum disorders within 2 hours. These agents differed in the effect on agitation over the 5-day course. Women were less responsive to treatment than men within the first 72 hours. Our results do not favor 1 of the oral antipsychotics for acute agitation in schizophrenia, which might be a result of the small sample size.

AUTHOR DISCLOSURE INFORMATION

S.W. has received speaker's fees from Sandoz and Janssen-Cilag. F.M. has received speaker's fees from Lilly and Novartis. H.H. has received speaker's fees from Eli Lilly, Janssen, and

Bristol-Myers Squibb. T.J.M. has received speaker's fees from AstraZeneca, Bristol-Myers Squibb, Janssen, Servier, Eli Lilly, Zeller Medical, and Sandoz; he is or has been a consultant to Eli Lilly, Lundbeck, Bristol-Myers Squibb, AstraZeneca, and Janssen. The other authors declare no conflicts of interest.

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